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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,586	09/11/2003	John P. Leonard	08702.0009-03000	4504

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EXAMINER	
MINNIFIELD, NITA M	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 05/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/659,586	LEONARD ET AL.	
	Examiner	Art Unit	
	N. M. Minnifield	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16,18-25 and 27-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16,18-25 and 27-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892) 2 pgs.
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5-00-

DETAILED ACTION

Response to Amendment

1. Applicants' amendment filed February 1, 2005 is acknowledged and has been entered. Claims 1-15, 17 and 26 have been canceled. Claims 16 and 25 have been amended. Claims 16, 18-25 and 27-33 are now pending in the present application. All rejections have been withdrawn in view of Applicants' amendment to the claims and/or comments, with the exception of those discussed below.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 21-24 and 30-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Claim 21 recites the limitation of "(a) blocks the formation of a heterodimer containing the 40 kD subunit; or (b) allows the formation of a heterodimer containing the 40 kD subunit, but blocks the activity of said heterodimer". Claim 30 recites the limitation of "(a) blocks the formation of a heterodimer containing the 35 kD subunit; or (b) allows the formation of a heterodimer containing the 35 kD subunit, but blocks the activity of said heterodimer". The specification does not set forth any written description of these limitations as now claimed. A review of page 8, line 5 through page 9, line 22 of the specification (as indicated by Applicants, in

related applications, to show support for the claim limitations) does not set forth support for the claim limitations. The specification, at pages 8-9, does not set forth a description or enablement for blocking the formation of the heterodimer or allowing the formation of the heterodimer.

This rejection is maintained for the reasons of record. Applicant's arguments filed February 1, 2005 have been fully considered but they are not persuasive.

Applicants disagree with the Examiner's understanding of the claimed invention. The claimed invention, is based at least in part, on the discovery that IL-12 induces an increase in levels of IFN-γ and/or TNF-α, which are involved in the promotion of many autoimmune conditions. The claimed invention solves this problem by providing antagonists of IL-12, use of which would be beneficial in treating an autoimmune condition promoted by an increase in the levels of IFN-γ and/or TNF-α. The claims at issue are drawn to method of treating an autoimmune condition promoted by an increase in levels of IFN-γ and/or TNF-α using IL-12 antagonists, specifically lL-12 antibodies, which bind either the 40 kD subunit of IL-12 (claims 21-24) or the 35 kD subunit of IL-12 (claims 30-33), and where such antibodies either block formation of a heterodimer containing the 40 kD or the 35 kD subunit or allow formation of the heterodimer but block its activity.

Applicants have asserted that the claim limitations are implicit in the disclosure of the specification as filed and that the specification provides adequate written description support for the broad genus of IL-12 antagonists, including IL-12 antibodies, which can bind the 40 kD and/or the 35 kD subunit of IL-12. For example, the specification discusses at page 6, line 21 that IL-12 antagonists include species that will bind IL-12 or biologically active fragments thereof. The specification further provides antibodies as an example of such antagonists, including monoclonal antibodies, polyclonal antibodies, chimeric antibodies and fragments thereof. See, specification at page 7, lines 1-5. The specification discusses that IL-12 is a heterodimeric protein comprised of 40 kD and 35 kD subunits. The specification further discusses that any form of IL-12 can be used in the methods of the invention. For example, IL-12 may be in the form of a heterodimer comprised of a 40 kD subunit disulfide-bonded to a 35 kD subunit or an individual subunit of lL-12 may be used. See, specification at page 8, lines 5-20. Accordingly, it would be clear to one of ordinary skill in the art that antagonists

that bind IL-12 or its fragments, may either bind IL-12 as a heterodimer, or they may bind a particular subunit of IL-12. Further, it is clear from the specification that those antagonists, which block IL-12 function would be desirable as such antagonists would prevent an increase in IFN-γ and/or TNF-α levels. Since IL-12 typically exists as a heterodimer, it would be clear to one of ordinary skill that either blocking the formation of such a heterodimer or blocking its activity would block IL-12 function.

The Examiner has reviewed the various sections of the specification that Applicants assert provide implicit disclosure for the claim limitations. However, this is not evident to the Examiner. Are Applicants interpreting "biologically active fragments thereof" to be the individual subunits, 40 kD and 35 kD? It is noted that Kim et al (2000) teaches that the subunits alone do not display any biological function; therefore it is unclear how they can be biologically active. The Examiner agrees that the specification discusses that IL-12 is a heterodimeric protein comprised of 40 kD and 35 kD subunits (p. 8, l.7-8). However, that section of the specification also states that "any form of IL-12 may be used, so long as that form of the IL-12 is capable of treating the desired autoimmune condition." (p. 8, l. 5-6) It is not clear how IL-12 can be used to treat autoimmune conditions when the state of the art teaches that IL-12 increases IFN-γ and/or TNF-α levels, which cause autoimmune inflammatory conditions. How is IL-12 or a IL-12 subunit that retains IL-12 biological activity used to treat an autoimmune condition, when the art teaches that IL-12 causes autoimmune conditions and that the subunits alone (separately) have no biological function? Further, which IL-12 subunit has this function? The specification does not teach or imply that antagonists to the subunits of IL-12 alone are able to treat an autoimmune condition. The specification does not indicate which subunit of IL-12 (40 kD or 35 kD) has the biological activity and thus when this activity is blocked by an

antagonist, would be able to treat an autoimmune condition. Applicants have asserted that as a result of various case law and USPTO guidelines that one of skill in the art would be able to recognize that Applicants' invention encompasses antagonists both which either block the formation of the heterodimer containing the 40 kD or the 35 kD subunit or which allow the formation of such a heterodimer but block its activity, as these antagonists would be useful in blocking IL-12 function. However, in view of the state of the art and the lack of clarity discussed above, one of skill in the art would not recognize that a compound that blocks an individual IL-12 subunit (35 kD or 40 kD) would be useful as antagonist in blocking the function of IL-12, since it appears that both subunits (40 kD and 35 kD, disulfide bonded) of IL-12 in the form of a heterodimer are necessary for IL-12 function.

4. Claims 16, 18-25 and 27-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are directed to a method for treating at least one autoimmune condition in a human subject, said method comprising administering to said subject a therapeutically effective amount of at least one antagonist that binds with a 40 kD subunit of IL-12, wherein said antagonist is chosen from at least one antibody (monoclonal or polyclonal) immunoreactive with the 40 kD subunit and at least one antibody fragment immunoreactive with the 40 kD subunit. Claims also recite the use of an antagonist that binds with a 35 kD subunit of IL-12 in the same manner. The

specification sets forth examples of IL-12 antagonist administration to mice for the treatment of MS (Example 1) and IDDM (Example 2). The specification has not taught such an antagonist or antibody that binds to the 40 kD or 35 kD subunit of the IL-12 that can be used to treat any autoimmune condition (for disease condition see claims 22-24 and 30-33) in a human.

The specification at pages 6-8 appear to be a mere paper protocol for a method of treating autoimmune conditions, for example RA, that administers an antibody that binds to a 40 kD or 35 kD subunit of IL-12 (IL-12 subunit "may be used"; pp. 6-8). Kim et al (2000) teaches that IL-12 levels reflect RA disease activity and that IL-12 is involved in the production of proinflammatory cytokines. An IL-12 blockade (i.e. anti-IL-12 antibodies) could be useful for the treatment of RA. Kim et al also teaches that the IL-12 is composed of the p35 and p40 subunits, but that neither of these (p35 or p40) subunits has been found to display any significant biological function alone (p. 175). Further, Benson et al, 2002 appears to indicate that IL-12 may not have a dominant role in chronic autoimmune diseases but rather IL-23. The IL-12p40 is shared by IL-23, a heterodimeric cytokine. Benson et al found that IL-12 specific neutralization had no beneficial effect on progression of experimental autoimmune encephalomyelitis (EAE), but that neutralization of both IL-12 and IL-23 effectively ameliorated EAE clinical signs. Therefore it is difficult to predict which antibody to the subunits of these cytokines (IL-12 or IL-23) or epitopes of the subunits of these cytokines binding to IL-12 are effective in a method of treating autoimmune diseases, without experimental evidence (see also Fox 2000, p. 237; Becher et al 2002, p. 493).

It is noted that the specification defines "treating" as curing, ameliorating, delaying or preventing onset of, preventing recurrence or relapse of autoimmune conditions or diseases and defines these conditions or diseases (see p. 3, l. 16 to p. 4, l. 3). However, the specification has not set forth enablement for the scope of treating autoimmune conditions as defined by Applicants' specification. Further, the state of the art with regard to preventing autoimmune conditions is unpredictable. There are no known compositions that can be administered to a subject that will prevent an autoimmune condition or disease (multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitus, and autoimmune inflammatory eye disease). Adorini teaches that IL-12-dependent Th1 responses have been implicated in a number of experimental autoimmune disorders (IDDM, EAE, collagen-induced arthritis, experimental allergic uveoretinitis, granulomatous colitis, experimental autoimmune myasthenia gravis, and thyroiditis (p. 17, col. 2). Anti-IL-12 mAb treatment prevents superantigen-induced EAE and subsequent replases (p. 17). "These findings suggest that targeting IL-12 may prove beneficial in some forms of MS, and it is likely that IL-12 antagonists can be useful in other autoimmune conditions, such as inflammatory bowel disease. Given the critical role of IL-12 in the induction of Th1-mediated autoimmune diseases, IL-12 antagonists could be candidates for immunointervention." (p. 17). Although Adorini suggests possibility of IL-12 antagonists as candidates for immunointervention, the state of the art has not shown definitively that IL-12 antagonists or antagonists (i.e. antibodies) that bind the 40 kD subunit of IL-12 or 35 kD subunit of IL-12 can be

used to treat or prevent the numerous autoimmune conditions or diseases as claimed by Applicants. The specification does not enable the claimed invention.

This rejection is maintained for the reasons of record. Applicants have Applicant's arguments filed February 1, 2004 have been fully considered but they are not persuasive.

Applicants have asserted that the references cited by the Examiner provide enabling disclosure for the antagonists, which bind the 40 kD subunit to treat various autoimmune diseases. The Examiner notes that the cited references (Kim, Fox et al, and Adorini; see also Yadav et al, 2003) all appear to suggest that antagonists, which bind IL-12 can be used to treat autoimmune diseases or conditions. Further, the Examiner is aware that Applicants now claim only those autoimmune conditions or disease, which are promoted by an increase in IFN-γ and/or TNF-α levels. The current references would still apply. The pending claims are directed to a method where an antagonist to a IL-12 subunit (i.e. 35 kD or 40 kD) are being administered to treat an autoimmune disease or condition, which is promoted by an increase in IFN-γ and/or TNF-α levels. The state of the art as previously indicated teaches that the IL-12, a heterodimer of p40 and p35 that are disulfate-bonded causes increases in IFN-γ and/or TNF-α levels and that this increase cause an autoimmune disease or condition. The art does not teach that the use of an antagonist to an individual subunit of IL-12, p40 or p35, can be used to treat an autoimmune condition or disease. In fact the art teaches that, individually these subunitsdo not have a function. Therefore a compound that binds to one of the subunits, individually, would not be able to treat an

autoimmune condition, since blocking of the IL-12 heterodimer is necessary to treat an autoimmune condition.

Applicants indicate that Wysocka et al and Neurath et al have been provided (courtesy copy) for Examiner consideration regarding antibodies to the subunits. However, these references are not found in the application. The Examiner will consider any references that Applicants provide.

With regard to antagonists, which bind the 35 kD subunit of IL-12, Applicants have asserted that even if a nonfunctional variant exists, it does not necessarily render a claim nonenabled. *Atlas Powder Co. v. E.I. dupont de Nemous & Co.*, 750 F.2d 1569, 1577, 224 U.S.P.Q. 409, 414 (Fed. Cir. 1984)., MPEP 2164.08(b). The specification provides screening assays and animal models, that can be used for testing antibodies that bind IL-12 for their ability to treat autoimmune conditions promoted by an increase in IFN-γ and/or TNF-α levels. However, it is noted that the claims are specifically directed to a method for treating at least one autoimmune condition promoted by an increase in IFN-γ and/or TNF-α levels in a human subject, said method comprising administering to said subject a therapeutically effective amount of at least one antagonist that binds with a 35 kD subunit of IL-12, wherein said antagonist is chosen from at least one antibody immunoreactive with the 35 kD subunit and at least one antibody fragment immunoreactive with the 35 kD subunit. Independent claim 25 is not directed to a screening assay or producing antibodies. The preamble specifically states that it is a method for treating. When a method is claimed it should be enabled. However, this situation would only apply if Applicants claims were directed to a product. A product, for example such as an antagonist that binds with a 35 kD subunit of IL-12. In this situation nonfunctional variants may potentially

exist, but does not necessarily render a claim nonenabled. There would be other uses for the product as asserted by Applicants. Again, Applicants have claimed a method of treating an autoimmune condition.

5. Claims 16, 18-22 and 27-31 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 16 and 22 of copending Application No. 09/512701 (now US Patent 6830751). Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications claim a method of administering to a subject a therapeutically effective amount of an antibody that binds a 40 kD subunit of IL-12 or 35 kD subunit of IL-12 for the purpose of treating an autoimmune condition.

This rejection has been maintained for the reasons of record. It is noted that Application 01/512701 has been patented and is now US Patent 6830751. Applicants have Applicant's arguments filed February 1, 2004 have been fully considered but they are not persuasive. "Applicants respectfully traverse this rejection, but, at this time, ask that this rejection be held in abeyance until allowable subject matter is determined. At that Applicants will consider whether to file a Terminal Disclaimer." (p. 18)

This rejection will be maintained until a properly filed Terminal Disclaimer has been filed.

6. No claims are allowed.

7. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette R.F. Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

N. M. Minnifield
Primary Examiner
Art Unit 1645

NMM
May 12, 2005